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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/385,918	HOEKSTRA ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 55-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 55-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *5/2/06* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1652.

2. Applicant's response to the Office Action mailed November 2, 2005 and July 26, 2006 on May 2, 2006 and August 25, 2006 is acknowledged.

Claim Disposition

3. Claims 1-10 and 55-59 are pending and are under examination.

Withdrawn Claim Objections

4. Previous objections to the claims are withdrawn by virtue of submission of an amendment.

Drawing

5. The drawings filed on May 2, 2006 have been accepted.

Maintained and Amended-Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-10 and 55-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for methods using a HECT E3 ubiquitin ligase domain, does not reasonably provide enablement for methods using variants of either such a domain or of a polypeptide comprising such a domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of variants thereof. The instant specification and claims identify polypeptides comprising a HECT E3 ubiquitin ligase WW domain and Smad PY motif, however, no conserved domains or structural characteristics are provided for the claimed variants thereof. Neither the instant specification or claims provide any indication as to where in

the sequence the variability will occur or demonstration that the variability encompassed in the claims is tolerated by the claimed sequences. A skilled artisan would have to engage in undue experimentation to construct said variants and test same for activity or the desired properties of the native proteins.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is

encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. The art is very clear on the fact that modifications to a protein's structure can affect the protein's structure function relationship. For example, Guo et al. (PNAS, vol. 101, no.25, pages 9205-9210, 2004) disclose that a third of single amino acid changes would completely inactivate the average protein and the more substitutions made the more probability that the protein will be inactivated. Thus, this gives the sense of what one of skill in the art can expect when a claim embraces fragments with up to 10, 20, 30, 40 or more amino acid changes and how many mutants one of skill in the art can test in such an endeavor. Note that the claims recite the open language comprising which puts no limit on the size of the variant/fragment.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. While recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine

experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure. It is noted that the claims recite "is not substantially diminished" with regard to the desired properties in the protein, however, the statement on its own is insufficient absent evidence. Page 14 of the specification discloses that substantially diminished is exemplified by "enhanced, unchanged or diminished by no more than 10%" relative to the native WW domain sequence. Note that diminished and the terms enhanced or unchanged are not synonymous. Additionally, "diminished by no more than 10%", includes a lot of variability, which is not supported by the instant specification. For example, SEQ ID NO:1 could have approximately 11 residues varied, whether by deletion, substitution, addition etc., and there is no indication of whether it would be 11 contiguous residues or any 11 residues in the sequence. There is no demonstration in the instant specification of said sequences retaining function.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variants. The nature and properties of the claims are difficult to ascertain from the example provided as one of skill in the art would have to engage in undue experimentation to construct the unlimited amount of variants of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of variants. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record.

This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)*. Therefore, absent direction/guidance regarding whether the structure of the polypeptides can tolerate the modifications contemplated a non-functional protein may result and one of skill in the art would not be able to practice the claimed invention commensurate in scope with the claims. In addition, absent direction/guidance regarding characteristics of the variants one of skill in the art would not be able to make the claimed variants thereof.

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible variants to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

7. Claims 1-10 and 55-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification and claims identify polypeptides comprising a HECT E3 ubiquitin ligase WW domain and Smad PY motif and includes variants thereof, however, no conserved domains or structural characteristics are provided for the claimed variants. Neither the instant specification or claims provide any indication as to where in the sequence the variability will occur or demonstration that the variability encompassed in the claims is tolerated by the claimed sequences. Therefore, the skilled artisan cannot envision the detailed chemical structure of the claimed variant polypeptides, thus, claims reciting said variants lacks adequate written description. In addition, the claimed methods do not provide a clear nexus between BMP-mediated signaling and the HECT E3 ubiquitin ligase WW domain and Smad.

Additionally, the instant specification does not demonstrate possession of said variant polypeptides. The claims encompass a large genus of variants. The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or

chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The claimed genus of variant polypeptides could include non-functional proteins or proteins with a different function than the one described. Further, *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Withdrawn-Basis For NonStatutory Double Patenting

8. Previous rejections to the claims for Obvious-type Double patenting is withdrawn by virtue of applicant's arguments.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102 (f) or (g) prior art under 35 U.S.C. 103 (a).

10. Claims 1-2, 4 and 55 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Pirozzi et al. (U.S. Patent No. 6,011,137, April 3, 1996), based on the broad recitation of variant thereof.

Pirozzi et al. teach methods and assays to screen compounds that are agonist or antagonist (inhibitors) of the interaction of a polypeptide having a WW domain by using a candidate compound (see column 7). Moreover, it is known in the prior art that the WW domain is involved in cell signaling and growth regulation or the organization of the cytoskeleton. Pirozzi et al. teach the sequence set forth in SEQ ID NO: 2 with a 75% sequence identity, a variant thereof (see the alignment) and teach the motif "PPPY" which can be construed as a variant thereof of the sequence set forth in SEQ ID NOS: 15, 16 and 18 (Smad PY motif). Pirozzi et al. does not teach a method to specifically screen for an agent that modulates BMP-mediated signaling, however, the screening method of Pirozzi et al. absent evidence to the contrary would effectively screen BMP-mediated signaling as it effectively screens for candidates affecting the WW domain involved in cell signaling.

Therefore, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention as a whole because Pirozzi et al. teach a screening method useful for detecting agonist/antagonist of the WW domain interaction with agents/candidate compound and the art recognizes the involvement of said domain with cell signaling. Thus, it would have been obvious to one of ordinary skill in the art to modify the teachings of Pirozzi et al. to use the interaction of Smad and a HECT E3 ubiquitin protein ligase to screen for effectors of BMP function. Further, the specification on page 2, disclose that "to date eight Smad protein have been identified and shown to participate in signal responses induced by TGF-Beta family members (i.e, BMP),

which serves as admitted prior art. Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

Response to Arguments

11. The response filed on May 2, 2006 has been considered. Note that the rejections of record under 35 USC 112, first paragraph and 103 remains.

Regarding the art rejection under 35 U.S.C. 112, first paragraph enablement, applicant on page 9 state that at the time the application was filed it was routine for the skilled in the art to prepare and screen large numbers of polypeptide variants. This argument is not persuasive because the claims broadly read on any variant thereof of the recited sequences and the instant specification lacks support for the full scope of the claims. The claims recite variants and the language "is not substantially diminished relative to the HECT E3 ubiquitin ligase", however, a mere statement absent evidence bears no weight. The specification on page 14 provides a definition, which is exemplary and not limiting, thus doesn't breathe life into the claims. Further, the definition of "no more than 10%" for substantially diminished leaves room for a lot of variability not supported by the instant specification. Thus, the issue is that the claims are not commensurate in scope with the instant specification and the make and test invitation in light of predictability in the art for the claimed variants. It is not routine in the art to make and test all the variants encompassed in the claims, which constitutes undue experimentation. No guidance is provided as to conserved regions or where in the sequence modifications will occur. Claim 1 for example, recites, "a first polypeptide comprising a HECT E3 ubiquitin ligase WW domain; SEQ

ID NO:1, 2, 3, 4, 5, ...or 13, or a variant thereof..." and there is not indication in the claim that what the structure of the variant thereof looks like. In fact the HECT E3 ubiquitin ligase WW domain is not necessarily tied to the sequences recited in the claim as no real connection is made such as ""a HECT E3 ubiquitin ligase WW domain set forth in SEQ ID NOS: 1, 2, 3, 4, ...or 13". Further, the recitation of the functional language does not endow function to the broad variant thereof language as there is no guarantee that the structure will retain function once modified. Thus, the rejection remains.

Moreover, as applicant has not demonstrated possession of all the variants encompassed by the claims, the written description rejection under 35 U.S.C. 112, first paragraph remains. Applicant on page 11 state that the specification clearly conveys to one having skill in the art that they were in possession of the claimed invention at the time the application was filed. This argument is not persuasive as the issue at hand is that the claims encompass a genus of proteins not adequately described and for which the specification does not provide a representative number of species for the claimed genus. Applicants arguments have been considered in full but are not persuasive, as a skilled artisan cannot envision the detailed chemical structure of the large variable genus of proteins encompassed by the claims and no correlation is made between structure and function for said genus.

Note that the rejection under 35 U.S.C. 103 remains because the requirement is a mere teaching or suggestion in the art. Applicant's arguments presented on pages 14+ have been considered, however, based on the breath of the claims the cited reference remains relevant. Applicant admits on page 14 that the Pirozzi discloses assays that affect the WW domain-containing polypeptide, hence a modulator. Furthermore, the reference teaches a sequence that is

75% identical to the sequence set forth in SEQ ID N O:2 of the instant application and the claims recite "variant thereof". Thus, the rejection remains.

Conclusion

12. No claims are presently allowable.

13. Applicant's amendment necessitated the new/modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Primary Examiner 11/13/06

HOPE ROBINSON
PRIMARY EXAMINER